HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

ROBUST SUMMARIES

For the

Diethylbenzene-Rich Streams Category

Prepared by:

American Chemistry Council
Ethylbenzene Panel HPV Task Group
Diethylbenzene Subteam

October 1, 2002

BIODEGRADATION

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No.25340-17-4)
Purity:	Not specified
Remarks:	

Method

Method/guideline followed:	EC Method C. 4-C, 1992
Type:	CO_2 evolution test (aerobic)
GLP:	Yes
Year:	1995
Contact time:	35 days
Innoculum:	Activated sludge
Remarks:	The test apparatus consisted of six glass 4-liter Erlenmeyer flasks containing two liters of modified biochemical oxygen demand (BOD) water. The test system was activated sludge collected from the Downingtown Regional Water Pollution Control Center (Pennsylvania) and screened through a 2 mm sieve and adjusted to a target solids level of 2500 mg/liter by diluting with settled sludge effluent. The adjusted sludge was aerated in semi-continuous activated sludge (SCAS) units until used in the preparation of the inoculum added to all flasks (up to 24 hours prior to study initiation). The sludge was not exposed to the test substance in the laboratory prior to addition to the test flasks. Test substance was added directly to the flasks to a final concentration of 10 mg/liter.The flasks were placed on a rotary platform shaker and mixed at 110 $\pm$ 10 rpm for the duration of the study. Incubation temperature was 22.2 to 23.2 ^{o}C.

Results

Degradation % after time:	4.7 after 28 days; 5.5 after 35 days
Results:	Mixed diethylbenzene stream is not readily biodegradable.
Kinetics:	Not determined
Breakdown products:	Not determined
Remarks:	

Conclusions The biodegradation of mixed diethylbenzene under aerobic conditions has been adequately characterized.

Data Quality

Reliability (Klimisch):	1B
Remarks:	Reliable without restriction; comparable to guideline study.

References

Marks, K. H., Crapo, K. C. and Doi, J. (1995). EC: CO_2 Evolution Test on Polyethylbenzene [Mixed Diethylbenzenes]. Unpublished Report by Roy F. Weston, Inc, Study No. 95-056. Conducted for Chevron Research and Technology Company.

Other Available Reports

MITI, Japan. 1993. Unpublished Report [1,4-Diethylbenzene]. Test was performed in Chemicals Inspection and Testing Institute.
4B: Not assignable; only secondary literature.

Other

Last changed:	September 4, 2001
Remarks:	

ACUTE ORAL TOXICITY (A)

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	Not stated
Remarks:	

Method

Method/guideline followed:	FIFRA/TSCA guidelines
Type:	LD_{50}
GLP:	Not stated
Year:	1987
Species/Strain:	Sprague-Dawley rats
Sex:	male and female
No. of animals per sex per dose:	5
Vehicle:	None
Route of administration:	Oral/gastric intubation
Remarks:	At the start of experiment, animals were about 9 to 12 weeks of age with a weight of 292 to 355 grams for males, and 224 to 253 grams for females. Room temperature was 67 to 76°F, and relative humidity was between 30 to 70% during the study. Animals were observed for 14 days postdose.

Results

LD_{50} value:	= 2050 mg/kg (confidence range 1770 to 2330 mg/kg) Number of deaths: 1700 mg/kg = 1 dead on day 3 (1 male); 1 dead at day 6 (1 female) 2500 mg/kg = 91 dead at 23 hours (1 female); 6 dead on day 2 (5 males and 1 female); 2 dead day 3 (2 females) 3500 mg/kg = 1 dead at 23 hours (1 female); 1 dead at day 1 (1 male); 6 dead at day 2 (3 males and 3 females); 1 dead at day 3 (1 male); and 1 dead at day 5 (1 female) 5000 mg/kg = 2 dead at 23 hours (1 male and 1 female); 5 dead at day 2 (4 males and 1 female); and 3 dead at day 3 (3 females)
Remarks:	A variety of abnormal signs occurred on the day of dosing. Several animals exhibited hypoactivity, red nasal discharge, urinary staining, partially closed eyes, prostration, and decreased food consumption. Signs seen in a few animals (in most groups) included ataxia, tremors, clear nasal and oral discharges, wet rales, soft stool, fecal staining and abdominal griping. A few animals exhibited blue pigmentation and hypothermia on the day of dosing; by day 2 or 3, a majority of the survivors were exhibiting these signs. Postmortem examinations of animals which were found dead revealed a variety of changes, primarily blue pigmentation of all/most soft tissues and/or blue fluid in the gastrointestinal tract and urinary bladder. Other changes

seen in most animals which were found dead included changes in the stomach, intestine and urinary bladder which were suggestive of an irritant and/or corrosive effect

Conclusions

Data Quality

Reliability (Klimisch): 1B

Remarks: Reliable without restrictions; comparable to guideline study.

Reference

Biodynamics Inc. 1987. Acute Oral Toxicity Study in Rats. Unpublished report 4086-87. Submitted to EPA by Monsanto Inc., as EPA Doc. No. 8EHQ-0892-8828

Other Available Reports

Chevron. 1991. The Acute Oral Toxicity of Polyethylbenzene [Mixed Diethylbenzenes] in Male and Female Rats. Unpublished Report No. 90-18.
1A: Reliable without restrictions: guideline study.

MHW, Japan. 1993. Single Oral Toxicity Test of 1,4-Diethylbenzene in Rats. Unpublished Report for OECD-SIDS program.
4B: Not assignable; only secondary literature.

Other

Last changed: September 4, 2001

Remarks:

ACUTE ORAL TOXICITY (B)

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	Not stated
Remarks:	

Method

Method/guideline followed:	FIFRA/TSCA guidelines
Type:	LD_{50}
GLP:	Yes
Year:	1990-1991
Species/Strain:	Sprague-Dawley rats
Sex:	male and female
No. of animals per sex per dose:	5
Vehicle:	Not stated
Route of administration:	Oral/gastric intubation
Remarks:	At start of the experiment, males were 74 days old with a weight of 225 to 340 grams, and females were 81 days old with a weight of 170 to 254 grams. Room temperature was 17 - 23°C, and relative humidity was between 45 – 65% during the study. Animals were observed for 14 days postdose.

Results

LD_{50} value:	= 6900 mg/kg for males; and 4700 mg/kg for females (95% confidence limits of 3800 to 12100 g/kg) Number of deaths: 3400 mg/kg = males and females: no deaths 4300 mg/kg = 1 dead on day 4 (males); 2 dead on day 3 (females) 5000 mg/kg = 1 dead on day 1 (males); 3 dead on days 2-3 (females) 7700 mg/kg = 3 dead on days 3-6 (males); 5 dead on days 2-4 (females)
Remarks:	Treated animals displayed similar patterns of toxicity that usually began with some variety of motor dysfunction (awkward gait, splayed fore- and hindlimbs) beginning approximately 6.5 hours after dosing. Tremors were also observed in some treated females of the 4300, 5000, and 7700 mg/kg dose groups, beginning 6 hours post-dosing. Cyanosis was observed in one treated male treated with 5000 mg/kg, 6.5 hours post-dosing. At Day 1, symptomology consistent with generalized central nervous system depression was observed in all treated animals. Several treated animals were found either comatose or unable to maintain normal posture. All treated animals exhibited reductions in spontaneous motor activity, abnormal righting reflexes, and decreases in responsiveness to extraneous sensory stimuli. Green urine was also observed on Day 1 in all dose groups.

Other signs of toxicity included but were not limited to reductions in the rate and depth of breathing, red nasal discharge, ocular and anogenital discharge, diarrhea, reduced pupil response, mydriasis, lacrimation, and partial palpebral closure. On Day 2, cyanosis developed within all treatment groups with the exception of females treated with 3400 and 4300 mg/kg. No treatment-related signs of toxicity were observed after Day 8 in surviving animals. At necropsy, dark fluid was found in the bladders of some animals treated with >3400 mg/kg. The gross appearance of these bladders were normal.

Conclusions

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restrictions; guideline study.

Reference

Chevron. 1991. The Acute Oral Toxicity of Polyethylbenzene [Mixed Diethylbenzenes] in Male and Female Rats. Unpublished Report No. 90-18.

Other Available Reports

Biodynamics Inc. 1987. Acute Oral Toxicity Study in Rats. Unpublished report BD-87-093. Submitted to EPA by Monsanto Inc., as EPA Doc. No. 8EHQ-0892-8828
1B: Reliable without restrictions; comparable to guideline study.

MHW, Japan. 1993. Single Oral Toxicity Test of 1,4-Diethylbenzene in Rats. Unpublished Report for OECD-SIDS program.
4B: Not assignable; only secondary literature.

Other

Last changed: September 4, 2001

Remarks:

ACUTE DERMAL TOXICITY (A)

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	Not stated
Remarks:	

Method

Method/guideline followed:	FIFRA/TSCA guidelines
Type:	LD_{50}
GLP:	Yes
Year:	1987
Species/Strain:	New Zealand White rabbits
Sex:	male and female
No. of animals per sex per dose:	5
Vehicle:	Not stated
Route of administration:	Dermal
Remarks:	At start of the experiment, animals were at least 8 weeks old. The males weighed between 2.3-2.6 kg, and the females weighed between 2.6-2.7 kg. Room temperature was 60-70°F, and relative humidity was between 30-70% during the study. Animals were observed for 14 days postdose.

Results

LD_{50} value:	= >5000 mg/kg
Remarks:	All animals exhibited body weight losses or no weight change at Day 7, but most gained weight between Days 7 and 14. Except for fissuring exhibited at a small portion of the dose site, in one animal, no severe dermal effects were seen. Decreased food consumption was exhibited by all ten animals on the day after dosing; by four animals on Day 4; and by one animal on Day 10.

Conclusions

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restrictions; guideline study.

Reference

Biodynamics Inc. 1987. Acute Dermal Toxicity Study in Rabbits. Unpublished report 4087-87. Submitted to EPA by Monsanto Inc., as EPA Doc. No. 8EHQ-0892-8828

Other Available Reports

Chevron, 1991. The acute dermal toxicity of polyethylbenzene [Mixed Diethylbenzenes] (MF-335) in rats. Unpublished Report. Study Number CEHC 3172, Chevron Environmental Health Center, Richmond, CA.

Other

Last changed: September 13, 2001
Remarks:

ACUTE DERMAL TOXICITY (B)

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	Not stated
Remarks:	

Method

Method/guideline followed:	FIFRA/TSCA guidelines
Type:	LD_{50}
GLP:	Yes
Year:	1990
Species/Strain:	Sprague-Dawley rats
Sex:	male and female
No. of animals per sex per dose:	5
Vehicle:	None
Route of administration:	Dermal
Remarks:	At start of the experiment, males were 71 weeks old and the females were 77 weeks old. The males weighed between 346 and 380 grams, and the females weighed between 228 and 266 grams. Room temperature was 20-22^{o}C, and relative humidity was between 34-56% during the study. Animals were observed for 14 days postdose.

Results

LD_{50} value:	= >2000 mg/kg
Remarks:	Compound-related signs of toxicity were limited to a yellow anogenital discharge in a single treated male. Skin irritation consisting of red, swollen and scabbed skin was more persistent and severe in treated animals than in controls. A significant decrease in mean body weight gain was observed in treated males on Days 0-2.

Conclusions

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restrictions; guideline study.

Reference

Chevron, 1991. The acute dermal toxicity of polyethylbenzene [Mixed Diethylbenzenes] (MF-335) in rats. Unpublished Report. Study Number CEHC 3172, Chevron Environmental Health Center, Richmond, CA.

Other Available Reports

Biodynamics Inc. 1987. Acute Dermal Toxicity Study in Rabbits. Unpublished report 4087-87. Submitted to EPA by Monsanto Inc., as EPA Doc. No. 8EHQ-0892-8828

Other

Last changed:	September 13, 2001
Remarks:	

REPEATED DOSE TOXICITY (A)

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	Not stated
Remarks:	

Method

Method/guideline followed:	EPA Guidelines
Test type:	Inhalation
GLP:	Yes
Year:	1991-1992
Species:	Rat
Strain:	Sprague-Dawley
Route of administration:	Inhalation
Duration of test:	3 months
Doses/concentration levels:	200, 600, and 1200 mg/m^3
Sex:	Male and female
Exposure period:	10 weeks (mixture) and 8 weeks (isomers)
Frequency of treatment:	6 hours/day, five days/week
Control group and treatment:	Concurrent
Postexposure observation period:	None
Statistical methods:	Dunnett's Multiple Comparison Test (two-tailed) for inlife body weights. Hematology data, clinical chemistry data, terminal body weights, absolute organ weights and organ/body weight ratios were evaluated by decision-tree statistical analyses which, depending on the results of tests for normality and homogeneity of variances (Bartlett's Test), utililized either parametric (Dunnett;s Test and Linear Regression) or non-parametric (Kruskal-Wallis, Jonckheere's and/or Mann-Whitney Tests) routines to detect differences and analyze for trends. Fisher's Exact Test (one-tailed) was used for incidence of microscopic lesions
Remarks:	There were 10 rats/group. The mean analytical concentrations were 0, 190, 610, and 1400 mg/m^3. Each exposure level was sampled four times daily, and the control chamber was sampled weekly, for test material concentration. Animals were checked twice daily for mortality and following each exposure for gross signs of toxicity. During exposure, visible animals were observed for signs of toxicity. Body weights and clinical observations were performed weekly. Opthalmic examinations were performed pretest on all animals and just prior to termination on control and high-exposure level animals. Clinicopathologic examinations were performed at termination. All animals were given a gross necropsy. All retained tissues from the control and high-exposure level groups were examined microscopically.

Results

NOAEL: 190 mg/m^3

Toxic response/effects: Decreased mean body weights in the high-dose group animals throughout the study. There were no abnormal clinical observations which were considered to be treatment-related. There were no ocular abnormalities attributed to administration of the test material. Treatment-related changes in hematologic parameters included moderate decreases in total white cell and lymphocyte counts in the mid- and high-exposure level males. Abnormal sera color (blue or blue-gray) was observed in high-exposure level animals of both sexes. Treatment-related changes in serum chemistry parameters included decreases in ALT, AST, and CPK in high-exposure level females and increases in potassium in high-level males an phosphorus in males from the high-exposure group and females from the mid- and high-exposure groups. An abnormal blue-gray color was observed in most tissues from all but one high-exposure animal. At the mid-exposure level, the same color was observed in brains of eight males and all females and in the urinary bladders of five females and one male. This abnormal color probably resulted from the presence of the parent chemical or a metabolite in these tissues. However, there was no other gross or microscopic changes attributed to the test material.

Statistical results:

Remarks:

Conclusions Repeated exposures to Mixed Diethylbenzenes (CAS No. 25340-17-4) did not result in any target organ toxicity. This endpoint has been adequately covered.

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; EPA Guideline study.

Reference Kaempfe, T. A. and Thake, D. C. 1993. Three-Month Inhalation Study of MCS 2313 [Mixed Diethylbenzenes] in Sprague-Dawley Rats. Monsanto Environmental Health Laboratory Report No. MSL-12570.

Other Available Reports Gagnaire, F., Marignac, B., and de Ceaurriz, J. (1990) Diethylbenzene-induced sensorimotor neuropathy in rats. J. Applied Toxicology 10(2): 105-112.
3D: Not reliable. Relevant methodological deficiencies.

Gagniare, F., Ensminger A.,, Marignac, B., and De Ceaurriz (1991) Possible involvement of 1,2-diacetylbenzene in diethylbenzene-induced neuropathy in rats. J. Appl. Toxicology 11(4) 261-268.
3D: Not reliable. Relevant methodological deficiencies.

Gagnaire, F., Becker, M. N., Marignac, B., Bonnet, P., and DeCeaurriz, J. (1992) Diethylbenzene inhalation-induced electrophysiological deficits in peripheral nerves and changes in brainstem auditory evoked potential in rats. J. Applied Toxicology 12(5): 335-342.
3D: Not reliable. Relevant methodological deficiencies.

Gagnaire, F., Becker, M. N., and De Ceaurriz, J. (1992) Alteration of brainstem auditory evoked potentials in diethylbenzene and diacetylbenzene-treated rats. J. Applied Toxicology 12(5): 343-350.
3D: Not reliable. Relevant methodological deficiencies.

MHW, Japan (1993) Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 1,4-Diethylbenzene. Unpublished Report for OECD-SIDS program.
4A: Not assignable; only short abstract available.

Other

Last changed: September 4, 2001
Remark:

REPEATED DOSE TOXICITY (B)

Test Substance

Identity:	Diethylbenzene (DEB) mixture (approx. 7% 1,2-diethylbenzene, 58% 1,3-diethylbenzene 35% 1,4-diethylbenzene) or individual diethylbenzene isomers
Purity:	95% 1,2-diethylbenzene, 99% 1,3-diethylbenzene, 96% 1,4-diethylbenzene
Remarks:	

Method

Method/guideline followed:	Not stated
Test type:	Oral
GLP:	No
Year:	
Species:	Rat
Strain:	Sprague-Dawley
Route of administration:	Oral gavage
Duration of test:	8 or 10 weeks
Doses/concentration levels:	500 or 750 mg/kg (in olive oil) for DEB mixture; 100 mg/kg for 1,2-diethylbenzene; and 500 mg/kg for 1,3- and 1,4-diethybenzene
Sex:	No specified
Exposure period:	10 weeks (mixture) and 8 weeks (isomers)
Frequency of treatment:	5 days/week (mixture and 1,3- and 1,4-diethylbenzene isomers); 4 days/week (1,2-diethylbenzene)
Control group and treatment:	Concurrent, given olive oil vehicle
Postexposure observation period:	8 weeks (isomer study only)
Statistical methods:	Differences in mean body weight, motor and sensory conduction velocities, and amplitude of the sensory action potential between experimental and control groups were analyzed using Student's t-test for independent data. Mean electrophysiolgoical deficits in the tail nerve were also analyzed, as a function of the length of treatment, by least-squares regression.
Remarks:	There were 12 rats/group. Rats were subjected to neurophysiological measurements every week during the treatment period. The survivors were kept for observation and neurophysiological measurements during the post-exposure period. The motor conduction velocity (MCV) and sensory conduction velocity (SCV) of the tail nerve and the amplitude of the sensory action potential (ASAP) were adopted as parameters for testing peripheral nerve function in rats.

Results

LOAEL:	500 mg/kg (DEB mixture); and 100 mg/kg (1,2-diethylbenzene)
NOAEL:	500 mg/kg (1,3- and 1,4-diethylbenzene)
Toxic response/effects:	Described below

Statistical results: Described below

Remarks: Diethylbenzene mixture

Rats given diethylbenzene (DEB) mixture with either 500 or 750 mg/kg exhibited a blue discoloration of the skin and urine as soon as the 3rd day of treatment. A significant reduction in weight gain was observed from the first week of treatment in the group treated with 750 mg/kg. Two animals died in the 750 mg/kg dose group during the first week of treatment. Two rats died in the 500 mg/kg group during the 4th and 7th weeks of treatment. No animals died in the control group. Rats in the DEB-dosed groups developed severe weakness in hind limbs and disturbances in gait from the 4th week of treatment. This weakness got worse in the following weeks, resulting in a complete paralysis of the hind limbs for some rats. There was a time-dependent decrease in MCV, SCV, and ASAP.

Diethylbenzene isomers

Rats given 1,2-diethylbenzene developed the same symptoms (decreased body weight, blue discoloration of skin and urine, weakness of hind limbs, paralysis) as those described for the diethylbenzene mixture. One rat died in the first week of treatment and another died in the 5th week of treatment. 1,3- and 1,4-Diethylbenzene-treated rats did not display any signs of neurotoxicity or any other signs of systemic toxicity. During the recovery period, the 1,2-diethylbenzene treated rats regained weight, became more mobile but presented trailing hind limbs, when attempting to walk. On the 4th week of recovery, all animals treated with 1,2-diethylbenzene succeeded in standing up. A time-dependent decrease in MCV, SCV, and ASAP was observed in animals dosed with 1,2-diethylbenzene, but not with 1,3- or 1,4-diethylbenzene.

Conclusions

Oral exposure to diethylbenzene mixture and 1,2-diethylbenzene produced adverse effects on the peripheral nervous system, whereas 1,3- and 1,4-diethylbenzene did not.

Data Quality

Reliability (Klimisch): 3D

Remarks: Not reliable. Relevant methodological deficiencies.

Reference

Gagnaire, F., Marignac, B., and de Ceaurriz, J. (1990) Diethylbenzene-induced sensorimotor neuropathy in rats. J. Applied Toxicology 10(2): 105-112.

Other Available Reports

Gagniare, F., Ensminger A.,, Marignac, B., and De Ceaurriz (1991) Possible involvement of 1,2-

diacetylbenzene in diethylbenzene-induced neuropathy in rats. J. Appl. Toxicology 11(4) 261-268.
3D: Not reliable. Relevant methodological deficiencies.

Gagnaire, F., Becker, M. N., Marignac, B., Bonnet, P., and DeCeaurriz, J. (1992) Diethylbenzene inhalation-induced electrophysiological deficits in peripheral nerves and changes in brainstem auditory evoked potential in rats. J. Applied Toxicology 12(5): 335-342.
3D: Not reliable. Relevant methodological deficiencies.

Gagnaire, F., Becker, M. N., and De Ceaurriz, J. (1992) Alteration of brainstem auditory evoked potentials in diethylbenzene and diacetylbenzene-treated rats. J. Applied Toxicology 12(5): 343-350.
3D: Not reliable. Relevant methodological deficiencies.

MHW, Japan (1993) Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 1,4-Diethylbenzene. Unpublished Report for OECD-SIDS program.
4A: Not assignable; only short abstract available.

Other

Last changed: September 13, 2001
Remark:

REPEATED DOSE TOXICITY (C)

Test Substance

Identity:	Diethylbenzene (DEB) mixture (approx. 6% 1,2-diethylbenzene, 66% 1,3-diethylbenzene 28% 1,4-diethylbenzene)
Purity:	Not stated
Remarks:	

Method

Method/guideline followed:	Not stated
Test type:	Inhalation
GLP:	No
Year:	
Species:	Rat
Strain:	Sprague-Dawley
Route of administration:	Inhalation
Duration of test:	18 weeks
Doses/concentration levels:	500, 700, and 900 ppm in experiment A; 600 and 800 ppm in experiment B
Exposure period:	18 weeks
Frequency of treatment:	6 hours/day, 5 days/week
Control group and treatment:	Concurrent
Postexposure observation period:	6 or 7 weeks
Statistical methods:	Statistical differences among groups were evaluated for each variable on each session by one-way analysis of variance. *Post hoc* individual mean comparisons were made with Duncan's multiple range test.
Remarks:	There were 12 rats/group in experiment A and 15 rats/group in experiment B. Rats were subjected to neurophysiological measurements every two weeks during the entire exposure period in experiment A, and every two weeks for the first 9 weeks of exposure in experiment B and then every three weeks thereafter. The survivors were kept for observation and neurophysiological measurements during the post-exposure period. The motor conduction velocity (MCV) and sensory conduction velocity (SCV) of the tail nerve and the amplitude of the sensory action potential (ASAP) were adopted as parameters for testing peripheral nerve function in rats in experiment A. In experiment B, only brainstem auditory evoked potential (BAEP) was measured.

Results

LOAEL:	500 ppm
Toxic response/effects:	Described below
Statistical results:	Described below
Remarks:	Experiment A

Exposure to DEB reduced weight gain from the first week of exposure in each group. There was no mortality in the control, 500 or 700 ppm exposed groups. In the 900 ppm group, one animal was euthanized on the fifth week of exposure due to an abcess at the neck. The animals of the 700 and 900 ppm exposed groups were prostrate during the exposure period but recovered a few hours after the end of the exposure period. Rats in the all DEB-exposed groups developed blue skin discoloration after three weeks of exposure. No animal in any group exhibited disturbances in gait or other signs of neurotoxicity. There was a time- and concentration-dependent decrease in MCV, SCV, and ASAP, which did not completely reversed during the 6-week recovery period.

Experiment B

Weight gain was reduced in the DEB-exposed groups. From the third week of exposure, the DEB-exposed groups exhibited the blue skin discoloration. At the end of the exposure period, some animals exhibited disturbances in gait and one animal in the 800 ppm group had partial paralysis in the hindlimbs. Two animals died in the 800 ppm group during the exposure period, and 8 animals/group had to be euthanized during the study because they lost their head plugs during the recording sessions. There was a time- and concentration dependent increase in both the peak latencies of all BAEP components and the interpeak (I-V) differences. Partial, but not complete reversal, occurred during the 7-week recovery period.

Conclusions

Inhalation exposure to diethylbenzene mixtures appear to have adverse effects on the peripheral and central nervous system. There seems to be, however, some inconsistences between the two experiments with regards to the clinical signs of peripheral nervous system damage. The authors proposed that this difference may be due to the age of the rats used in these two expeirments, 9-and 19-week old, respectively.

Data Quality

Reliability (Klimisch): 3D

Remarks: Not reliable. Relevant methodological deficiencies.

Reference

Gagnaire, F., Becker, M. N., Marignac, B., Bonnet, P., and De Ceaurriz, J. (1992) Diethylbenzene inhalation-induced electrophysiological deficits in peripheral nerves and changes in brainstem auditory evoked

potentials in rats. J. Applied Toxicology 12(5): 335-342.

Other Available Reports

Kaempfe, T. A. and Thake, D. C. Three-Month Inhalation Study of MCS 2313 [Mixed Diethylbenzenes] in Sprague-Dawley Rats. Monsanto Environmental Health Laboratory Report No. MSL-12570.

Gagnaire, F., Marignac, B., and de Ceaurriz, J. (1990) Diethylbenzene-induced sensorimotor neuropathy in rats. J. Applied Toxicology 10(2) 105-112.
3D: Not reliable. Relevant methodological deficiencies.

Gagniare, F., Ensminger A.,, Marignac, B., and De Ceaurriz (1991) Possible involvement of 1,2-diacetylbenzene in diethylbenzene-induced neuropathy in rats. J. Appl. Toxicology 11(4) 261-268.
3D: Not reliable. Relevant methodological deficiencies.

Gagnaire, F., Becker, M. N., and De Ceaurriz, J. (1992) Alteration of brainstem auditory evoked potentials in diethylbenzene and diacetylbenzene-treated rats. J. Applied Toxicology 12(5): 343-350.
3D: Not reliable. Relevant methodological deficiencies.

MHW, Japan (1993) Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 1,4-Diethylbenzene. Unpublished Report for OECD-SIDS program.
4A: Not assignable; only short abstract available.

Other

Last changed: September 4, 2001
Remarks:

GENETIC TOXICITY *IN VITRO* (A)

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	
Remarks:	

Method

Method/guideline followed:	OECD Method No. 471
Type:	*Salmonella* reverse mutation assay
System of testing:	Bacterial
GLP:	Yes
Year:	1990
Species/Strain:	*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with S-9 activation and without S-9 activation
Metabolic activation:	Liver S-9 fraction from Aroclor 1254 pretreated (injected, ip) male Sprague-Dawley rats.
Concentrations tested:	0.003, 0.01, 0.033, 0.1, 0.333, 1.0, 3.33, 10.0 mg/plate
Statistical methods:	Not stated
Remarks:	Positive (2-aminoanthracene, 2-nitrofluorene, and sodium azide) and negative controls were included. Eight doses in addition to the concurrent solvent and positive controls were tested on each strain in the presence of S-9 mix or buffer. Three plates were used, and the results were confirmed in an independent experiment.

Results

Result:	Negative
Cytotoxic concentration:	$\geq$ 1 mg/plate
Genotoxic effects:	Negative
Statistical results:	Statistically significant increases in the number of revertants were observed for TA98 and TA100 in the presence of metabolic activation. These responses were not reproducible and were, therefore, not considered to be biologically significant.
Remarks:	

Conclusions Mixed diethylbenzenes (25340-17-4) did not cause mutations to *S.* typhimurium in this *in vitro* genetic toxicity test. The bacterial mutation potential of mixed diethylbenzenes (25340-17-4) has been adequately characterized by this study.

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; OECD guideline study.

Reference

Chevron. 1991. Microbial/Microsome Reverse Mutation Plate Incorporation Assay with Polyethylbenzene [Mixed Diethylbenzenes] (MF-355). Unpublished Report No. 90-23.

Other Available Reports

Stankowski, L. F. 1988 Ames/*Salmonella* Plate Incorporation Assay. Pharmakon Research International, Inc. Study No. 301-MO-002-88. Conducted for Monsanto Company.
1A: Reliable without restriction; EPA guideline study.

Myers, C.A., and Fahey, P.M. (1989) In Vitro Cytogenetics Study on MCS 2313 (mixed diethylbenzene stream, CAS No. 25340-17-4). Conducted at Monsanto Company Environmental Health Laboratory, Report No. MSL-9002.
1A: Reliable without restriction; EPA guideline study.

MWH, Japan. 1993. Reverse Mutation Test of 1,4-Diethylbenzene on Bacteria. Unpublished Report for OECD-SIDS program.
4B: Not assignable; only secondary literature.

Other

Last changed: September 4, 2001

Remarks:

GENETIC TOXICITY *IN VITRO* (B)

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	Not specified
Remarks:	

Method

Method/guideline followed:	OECD Method No. 471
Type:	*E. coli*
System of testing:	Bacterial
GLP:	Yes
Year:	1990
Species/Strain:	*E.* coli WP2 uvrA with S-9 activation and without S-9 activation
Metabolic activation:	Liver S-9 fraction from Aroclor 1254 pretreated (injected, ip) male Sprague-Dawley rats.
Concentrations tested:	0.003, 0.01, 0.033, 0.1, 0.33, 1.0, 3.33, 10.0 mg/plate
Statistical methods:	Not stated.
Remarks:	Positive (2-aminoanthracene and ICR-191) and negative controls were included. Eight doses in addition to the concurrent solvent and positive controls were tested in the presence of S-9 mix or buffer. Three plates were used, and results were confirmed in an independent experiment.

Results

Result:	Negative
Cytotoxic concentration:	$\geq$ 1 mg/plate
Genotoxic effects:	Negative
Statistical results:	
Remarks:	Cytotoxicity was also observed in WP2 uvrA without S-9 at dose levels of 0.1 and 0.33 mg/plate in a single experiment. Since WP2 uvrA is generally more resistant to toxicity than the *Salmonella* strains (which tested in the same experiment; see 5.5A), and the toxicity was observed also in the positive controls where it was not expected, it was concluded that the cytotoxic response in WP2 uvrA without activation at 0.1 and 0.33 mg/plate was probably not treatment-related.

Conclusions

Mixed diethylbenzenes (25340-17-4) did not cause mutations to *E.* coli in this *in vitro* genetic toxicity test. The bacterial mutation potential of mixed diethylbenzenes (25340-17-4) has been adequately characterized by this study.

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; OECD guideline study.

Reference

Chevron. 1991. Microbial/Microsome Reverse Mutation Plate Incorporation Assay with Polyethylbenzene [Mixed Diethylbenzenes] (MF-355). Unpublished Report No. 90-23.

Other Available Reports

Stankowski, L. F. 1988 Ames/*Salmonella* Plate Incorporation Assay. Pharmakon Research International, Inc. Study No. 301-MO-002-88. Conducted for Monsanto Company.
1A: Reliable without restriction; EPA guideline study.

Myers, C.A., and Fahey, P.M. (1989) In Vitro Cytogenetics Study on MCS 2313 (mixed diethylbenzene stream, CAS No. 25340-17-4). Conducted at Monsanto Company Environmental Health Laboratory, Report No. MSL-9002.
1A: Reliable without restriction; EPA guideline study.

MWH, Japan. 1993. Reverse Mutation Test of 1,4-Diethylbenzene on Bacteria. Unpublished Report for OECD-SIDS program.
4B: Not assignable; only secondary literature.

Other

Last changed: September 4, 2001
Remarks:

GENETIC TOXICITY *IN VITRO* (C)

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	
Remarks:	

Method

Method/guideline followed:	EPA Guidelines
Type:	*Salmonella* reverse mutation assay
System of testing:	Bacterial
GLP:	Yes
Year:	1988
Species/Strain:	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 with S-9 activation and without S-9 activation
Metabolic activation:	Liver S-9 fraction from Aroclor 1254 pretreated male Sprague-Dawley rats.
Concentrations tested:	0.00167, 0.005, 0.0167, 0.05, 0.167, 0.5 mg/plate
Statistical methods:	Not stated
Remarks:	Positive (2-aminoacridine, 2-nitrofluorene, 2-antramine and sodium azide) and negative controls were included. Six doses in addition to the concurrent solvent and positive controls were tested on each strain in the presence of S-9 mix or buffer. Three plates were used, and the results were confirmed in an independent experiment.

Results

Result:	Negative
Cytotoxic concentration:	$\geq$ 0.05 mg/plate
Genotoxic effects:	Negative
Statistical results:	
Remarks:	

Conclusions

Mixed diethylbenzenes (25340-17-4) did not cause mutations to *S.* typhimurium in this *in vitro* genetic toxicity test. The bacterial mutation potential of mixed diethylbenzenes (25340-17-4) has been adequately characterized by this study.

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

Reference

Stankowski, L. F. 1988 Ames/*Salmonella* Plate Incorporation Assay. Pharmakon Research International, Inc. Study No. 301-MO-002-88. Conducted for Monsanto Company.

Other Available Reports

Chevron. 1991. Microbial/Microsome Reverse Mutation Plate Incorporation Assay with Polyethylbenzene [Mixed Diethylbenzenes] (MF-355). Unpublished Report No. 90-23.
1A: Reliable without restriction; OECD guideline study.

Myers, C.A., and Fahey, P.M. (1989) In Vitro Cytogenetics Study on MCS 2313 (mixed diethylbenzene stream, CAS No. 25340-17-4). Conducted at Monsanto Company Environmental Health Laboratory, Report No. MSL-9002.
1A: Reliable without restriction; EPA guideline study.

MWH, Japan. 1993. Reverse Mutation Test of 1,4-Diethylbenzene on Bacteria. Unpublished Report for OECD-SIDS program.
4B: Not assignable; only secondary literature.

Other

Last changed: September 4, 2001

Remarks:

GENETIC TOXICITY *IN VITRO* (D)

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	
Remarks:	

Method

Method/guideline followed:	EPA Guidelines
Type:	Chromosomal aberration assay
System of testing:	mammalian cells
GLP:	Yes
Year:	1988
Species/Strain:	Chinese Hamster Ovary cells with and without S-9 activation
Metabolic activation:	Liver S-9 fraction from Aroclor 1254 pretreated Sprague-Dawley rats.
Concentrations tested:	25, 40, 50, 60, and 75 ug/ml
Statistical methods:	Chi-square analysis was used to analyze the number of cells with structural aberrations. Dunnett's t-test was used to analyze structural aberrations per cell.
Remarks:	Positive (methyl methane sulfonate and cyclophosphamide) and negative controls were included. Five doses in addition to the concurrent solvent and positive controls were tested in the presence of S-9 mix or buffer. Duplicate samples per treatment condition were used and the cells were harvested at 12 an 24 hours after initiation of treatment.

Results

Cytotoxic concentration:	$\geq$ 50 ug/ml
Genotoxic effects:	Negative
Statistical results:	
Remarks:	

Conclusions

Mixed diethylbenzenes (25340-17-4) did not cause any statistically significant increase in the number of cells with structural aberrations or in the average structural aberrations per cell. The clastogenic potential of mixed diethylbenzenes (25340-17-4) has been adequately characterized by this study.

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; EPA guideline study.

Reference

Myers, C.A., and Fahey, P.M. (1989) In Vitro Cytogenetics Study on MCS 2313 (mixed diethylbenzene stream, CAS No. 25340-17-4). Conducted at Monsanto Company Environmental Health Laboratory, Report No. MSL-9002.

Other Available Reports

Chevron. 1991. Microbial/Microsome Reverse Mutation Plate Incorporation Assay with Polyethylbenzene [Mixed Diethylbenzenes] (MF-355). Unpublished Report No. 90-23.
1A: Reliable without restriction; OECD guideline study.

Stankowski, L. F. 1988 Ames/*Salmonella* Plate Incorporation Assay. Pharmakon Research International, Inc. Study No. 301-MO-002-88. Conducted for Monsanto Company.
1A: Reliable without restriction; EPA guideline study.

MWH, Japan. 1993. Reverse Mutation Test of 1,4-Diethylbenzene on Bacteria. Unpublished Report for OECD-SIDS program.
4B: Not assignable; only secondary literature.

Other

Last changed: September 4, 2001

Remarks:

GENETIC TOXICITY *IN VIVO*

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	Not specified
Remarks:	

Method

Method/guideline followed:	OECD Method No. 474
Type:	Micronuclei formation in bone marrow erythrocytes
GLP:	Yes
Year:	1990
Species:	Mouse
Strain:	CD-1
Sex:	Male and female
Route of administration:	Intraperitoneal
Doses/concentration levels:	1000, 2000, and 4000 mg/kg (diluted with peanut oil)
Exposure period:	Single dose
Statistical methods:	
Remarks:	Vehicle and positive controls were dosed intraperitoneally with peanut oil and cyclophosphamide, respectively. Number of animals: 18/sex/group, except for the positive control group (5/sex). Bone marrow smears, 5 animals/sex/dose, were made at approximately 24, 48, and 72 hours post-dosing, according to the method of Schmid (1976)[1]. The slides were fixed in methanol and stained with 5% Giemsa for approximately 20 minutes. The percentage of PCE was calculated by counting a total of >200 erythrocytes. On each slide, a total of 1000 PCEs were evaluated for the presence of micronuclei.

[1]Schmid, W (1976) The micronucleus test for cytogenetic analysis. In: A. Hollaender (Ed), Chemical Mutagens, vol. 4, pp. 31-53, Plenum, NY

Results

Cytotoxicity:	Cytotoxicity was noted in females dosed with 4000 mg/kg and sampled at 48 hours.
Genotoxic effects:	No treatment-related effect on increased micronucleated polychromatic erythroctyes in either sex.
NOEC or LOAEC:	1000 mg/kg
Statistical results:	No statistically significant differences between mixed diethylbenzene-exposed animals and controls.
Remarks:	Evidence of toxicity was found at $\geq$ 2000 mg/kg in both sexes. Clinical signs of toxicity observed were decreased motor activity, collapse, labored breathing, convulsions, and weakness. In addition, on Day 1, one male at 2000 mg/kg and three males and one female at 4000 mg/kg

	died before the scheduled sampling time; two moribund females at 4000 mg/kg were euthanized.
Conclusions	Under the conditions of this study, mixed diethylbenzene (25340-17-4) was considered non-genotoxic, since micronuclei were not induced in the bone marrow eythrocytes of mice.
Data Quality	
Reliability (Klimisch):	1A
Remarks:	Reliability without restriction; OECD guideline study.
References	Chevron. 1991. Micronucleus Assay in Mouse Bone Marrow Erythrocytes: Polyethylbenzene [Mixed Diethylbenzenes]. Unpublished Report No. 90-24.
Other Available Reports	MHW, Japan. 1993. In Vitro Chromosomal Aberration Test of 1,4-Diethylbenzene on Cultured Chinese Hamster Cells. Unpublished Report for the OECD-SIDS program. 4B: Not assignable; only secondary literature.
Other	
Last changed:	September 4, 2001
Remarks:	

REPRODUCTIVE TOXICITY (A)

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	Not stated
Remarks:	

Method

Method/guideline followed:	EPA Guidelines
Test type:	Inhalation
GLP:	Yes
Year:	1991-1992
Species:	Rat
Strain:	Sprague-Dawley
Route of administration:	Inhalation
Duration of test:	3 months
Doses/concentration levels:	200, 600, and 1200 mg/m^3
Exposure System:	Low exposure level test atmospheres were genererated using a Laskin-style nebulizer/spraybar positioned in the supply air chamber inlet. Test material was delivered using syringe pump. The mid- and high-exposure level test atmospheres were generated using a spray nozzle directed down from the top of the chamber. Test material was delivered for the mid- and high-level chambers with a valveless pump. The concentration of test material in the chambers was controlled by regulating the flowrate of the material from the pumps.
Sex:	Male and female
Exposure period:	10 weeks (mixture) and 8 weeks (isomers)
Frequency of treatment:	6 hours/day, five days/week
Control group and treatment:	Concurrent
Postexposure observation period:	None
Statistical methods:	Dunnett's Multiple Comparison Test (two-tailed) for in-life body weights. Absolute organ weights and organ/body weight ratios were evaluated by decision-tree statistical analyses which, depending on the results of tests for normality and homogeneity of variances (Bartlett's Test), utililized either parametric (Dunnett;s Test and Linear Regression) or non-parametric (Kruskal-Wallis, Jonckheere's and/or Mann-Whitney Tests) routines to detect differences and analyze for trends. Fisher's Exact Test (one-tailed) was used for incidence of microscopic lesions
Remarks:	There were 10 rats/group. The mean analytical concentrations were 0, 190, 610, and 1400 mg/m^3. Each exposure level was sampled four times daily, and the control chamber was sampled weekly, for test material concentration. Animals were checked twice daily for mortality and following each exposure for gross signs of toxicity. During exposure, visible

animals were observed for signs of toxicity. Body weights and clinical observations were performed weekly. All animals were given a gross necropsy. All retained tissues, including ovaries, pituitary, prostate, seminal vesicles, testes with epididymides, and uterus (corpus and cervix), from the control and high-exposure level groups were examined microscopically.

Results

NOAEL: 190 mg/m^3

Toxic response/effects: Decreased mean body weights in the high-dose group animals throughout the study. There were no abnormal clinical observations which were considered to be treatment-related. An abnormal blue-gray color was observed in most tissues from all but one high-exposure animal. At the mid-exposure level, the same color was observed in brains of eight males and all females and in the urinary bladders of five females and one male. This abnormal color probably resulted from the presence of the parent chemical or a metabolite in these tissues. However, there were no other gross or microscopic changes in the reproductive tissues attributed to the test material.

Statistical results:

Remarks:

Conclusions

Mixed Diethylbenzene Stream (25340-17-4) does not appear to target the reproductive organs in rats.

Data Quality

Reliability (Klimisch): 2C

Remarks: Reliable with restrictions; comparable to guideline study with acceptable restrictions.

Reference

Kaempfe, T. A. and Thake, D. C. Three-Month Inhalation Study of MCS 2313 [Mixed Diethylbenzenes] in Sprague-Dawley Rats. Monsanto Environmental Health Laboratory Report No. MSL-12570.

Other Available Reports

MHW, Japan (1993) Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 1,4-Diethylbenzene. Unpublished Report for OECD-SIDS program.

4A: Not assignable; only short abstract available.

Other

Last changed: September 4, 2001

Remark:

REPRODUCTIVE TOXICITY (B)

Test Substance

Identity:	1,4-Diethylbenzene (CAS No. 105-05-5)
Purity:	97.2%
Remarks:	

Method

Method/guideline followed:	OECD Guideline No. 422
Test type:	Oral gavage
GLP:	Yes
Year:	1993
Species:	Rat
Strain:	Sprague-Dawley
Route of administration:	Oral gavage
Duration of test:	Male: 44 days including 14 days before mating Female: 14 days before mating to lactation day 3
Doses/concentration levels:	30, 150, and 750 mg/kg
Sex:	Male and female
Exposure period:	Male: 44 days including 14 days before mating Female: 14 days before mating to lactation day 3
Frequency of treatment:	7 days/week
Control group and treatment:	Concurrent
Postexposure observation period:	None
Statistical methods:	Not stated
Remarks:	There were 12 rats/sex/group.

Results

NOAEL:	350 mg/kg/day?
Toxic response/effects:	Male and female copulation and fertility indices, pregnancy rates, and implantation sites were comparable among groups. The number of live and dead pups, the number of litters with live offspring, the mean litter size, and the male-to-female ratio were comparable among the groups on lactation day 0. There were no differences in mean pup weights across groups. No differences were found in external observations; and no remarkable findings were observed at necropsy in pups found dead prior to lactation day 4. Duration of gestation was slightly, but statistically significantly, increased in the 750 mg/kg group and there was a statistically significant decrease in pup survival on day 4 in the 750 mg/kg group; however, the investigators did not consider these findings treatment-related.
Statistical results:	
Remarks:	

Conclusions

1,4-Diethylbenzene (105-05-5) does not appear to be a reproductive toxicant, although a slight effect was observed on duration of gestation.

Data Quality

Reliability (Klimisch): 4A

Remarks: Not assignable; only short abstract available.

Reference

OECD-SIDS Dossier on 1,4-Diethylbenzene (CAS No. 105-05-5). MHW, Japan (1993) Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 1,4-Diethylbenzene. Unpublished Report for OECD-SIDS program.

Other Available Reports

Kaempfe, T. A. and Thake, D. C. Three-Month Inhalation Study of MCS 2313 [Mixed Diethylbenzenes] in Sprague-Dawley Rats. Monsanto Environmental Health Laboratory Report No. MSL-12570.
2C: Reliable with restrictions; comparable to guideline study with acceptable restrictions.

Other

Last changed: September 4, 2001

Remark:

DEVELOPMENTAL TOXICITY/TERATOGENICITY (A)

Test Substance

Identity:	Mixed Diethylbenzene Stream (CAS No. 25340-17-4)
Purity:	Not stated
Remarks:	

Method

Method/guideline followed:	EPA Guidelines
GLP:	Yes
Year:	1992
Species:	Rat
Strain:	Sprague-Dawley
Route of administration:	Oral gavage
Doses/concentration levels:	20, 100, 200 mg/kg/day (in corn oil)
Sex:	Female
Exposure period:	Day 6 through 15 of gestation
Frequency of treatment:	7 days/week
Control group and treatment:	Concurrent, received 5 ml/kg corn oil
Duration of test:	Day 20 of gestation
Statistical methods:	Continuous maternal and fetal data, including body weights, body weight gain, food consumption, number of fetuses, implantation sites and corpora lutea, were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's test. The Mann-Whitney U test was used to compare post-implantation loss and resorptions. Fetal sex ratios were analysed using the Chi-Square test. Fisher's Exact test was used to analyze the incidence and number of fetal malformations and variations utilizing the dam (litter) as the experimental unit.
Remarks:	Twenty-five female rats were assigned to each group. The animals were observed daily for clinical signs of toxicity. Body weights and food consumption were measured on gestation day 0, 6, 9, 12, 16, and 20. Surviving females were euthanized on gestation day 20 and subjected to cesarean section. Fetuses were individually weighed, sexed and examined for external, visceral and skeletal abnormalities.

Results

Maternal toxicity NOAEL:	= 20 mg/kg/day
Developmental toxicity NOAEL:	= 100 mg/kg/day
Actual dose received:	0, 20, 100, or 200 mg/kg/day
Maternal data:	There were no treatment-related mortality or clinical signs of toxicity. Mean maternal body weight gain and food consumption statistically reduced at the 100 and 200 mg/kg/day groups throughout the study. Greenish-blue discoloration of the amniotic sac was observed in a dose-related manner at the 100 and 200 mg/kg/day levels.

Fetal data:	Mean fetal body weight was statistically reduced at the 200 mg/kg/day level when compared to the control group. All other cesarean parameters were comparable among groups. No treatment-related malformations or developmental variations were observed.
Statistical results:	
Remarks:	

Conclusions

Oral gavage dosing with up to 200 mg/kg/day of mixed diethylbenzene (25340-17-4) did not produce a teratogenic response in rats. Maternal toxicity occurred at dosages that were lower than that which produced developmental toxicity.

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliability without restriction; EPA guideline study.

Reference

Mercieca, M. D. 1992 Teratology Study in Rats with MCS 2313 [mixed diethylbenzene]. Springborn Laboratories, Inc. Report No. 30344.228. Conducted for Monsanto Company.

Other Available Reports

Saillenfait, A. M.., Payan, J. P., Langonné. I., Gallissot, F., Sabaté, J. P., Beydon, D., and Fabry, J. P. (1999) Assessment of the developmental toxicity and placental transfer of 1,2-diethylbenzene in rats. Food Chemical Toxicol. 37: 1089-1096.
2B: Reliable with restrictions; basic data given, comparable to guidelines/standards.

MHW, Japan. 1993. Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 1,4-Diethylbenzene. Unpublished Report for the OECD-SIDS program.
4A: Not assignable; only short abstract available.

Other

Last changed:	September 4, 2001
Remarks:	

DEVELOPMENTAL TOXICITY/TERATOGENICITY (B)

Test Substance

Identity:	1,2-Diethylbenzene
Purity:	>99%
Remarks:	

Method

Method/guideline followed:	Not stated
GLP:	Not stated
Year:	
Species:	Rat
Strain:	Sprague-Dawley
Route of administration:	Oral gavage
Doses/concentration levels:	5, 15, 25, or 35 mg/kg/day
Sex:	Female
Exposure period:	Day 6 through 20 of gestation
Frequency of treatment:	7 days/week
Control group and treatment:	Concurrent, received 2 ml/kg corn oil
Duration of test:	Day 21 of gestation
Statistical methods:	Number of implantation sites and live fetuses, food consumption and various body weights were analyzed by one-way analysis of variance, followed by Dunnett's test if differences were found. The frequencies of non-surviving implants, resorptions, males, and anomalies among litters were evaluated by using Dixon-Massey test. Rates of pregnancy and incidence of litters with alterations were analyzed by using Fisher's test. Where applicable, least-squares analysis was carried out.
Remarks:	There were 28-29 female rats assigned to each group. All females were observed daily for clinical signs of toxicity. Food consumption was measured at 3-day intervals starting at gestation day (GD) 6. Maternal body weights were recorded on GD0, 6, 9, 12, 15, 18, 21. On GD 21, the females were euthanized and the uteri were removed and weighed. Uterine contents were examined to determine the number of implantation sites, resorptions, and dead/live fetuses. Live fetuses were weighed, sexed, and examined for external anomalies. Half of the live fetuses for each litter were examined for internal soft tissue changes and the other half were processes for skeletal staining.

Results

Maternal toxicity NOAEL:	= 5 mg/kg/day
Developmental toxicity NOAEL:	= 5 mg/kg/day
Actual dose received:	5, 15, 25, and 35 mg/kg/day
Maternal data:	No animals died during the study. Maternal weight gain was significantly reduced during GD 6-9 in the $\geq$ 15 mg/kg dose groups, and for GD 18-21 in the 35 mg/kg dose group. Females dose with $\geq$ 15 mg/kg had

	significant dose-related decreases in maternal weight gain for GD 6-21 and in corrected weight gain. Maternal food consumption was significantly depressed during the initial and final three days of treatment at ≥ 15 mg/kg. Depression in food consumption persisted during GD 9-12 in the 25 mg/kg dose group, and during GD 9-12 and GD 15-18 in the 35 mg/kg dose group. Overall, food consumption on GD 6-21 was significantly decreased in the 25 and 35 mg/kg dose groups. There were no significant effects on the average number of implantations and live fetuses, on the incidence of non-surviving implants per litter, or on the fetal sex ratio.
Fetal data:	Fetal body weights in the ≥ 15 mg/kg dose groups were significantly reduced, and were dose-related. There was no evidence of a treatment-related effect in any malformations or variations.
Statistical results:	
Remarks:	
Conclusions	Oral gavage dosing with up to 35 mg/kg/day 1,2-diethylbenzene produced reduced fetal body weights, but no teratogenic effects . Developmental toxicity occurred only at dosages that produced maternal toxicity.
Data Quality	
Reliability (Klimisch):	2B
Remarks:	Reliable with restrictions; basic data given, comparable to guidelines/standards.
Reference	Saillenfait, A. M.., Payan, J. P., Langonné. I., Gallissot, F., Sabaté, J. P., Beydon, D., and Fabry, J. P. (1999) Assessment of the developmental toxicity and placental transfer of 1,2-diethylbenzene in rats. Food Chemical Toxicol. 37: 1089-1096.
Other Available Reports	Mercieca, M. D. 1992 Teratology Study in Rats with MCS 2313 [mixed diethylbenzene]. Springborn Laboratories, Inc. Report No. 30344.228. Conducted for Monsanto Company. MHW, Japan. 1993. Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 1,4-Diethylbenzene. Unpublished Report for the OECD-SIDS program. 4A: Not assignable; only short abstract available.
Other	
Last changed:	September 4, 2001
Remarks:	